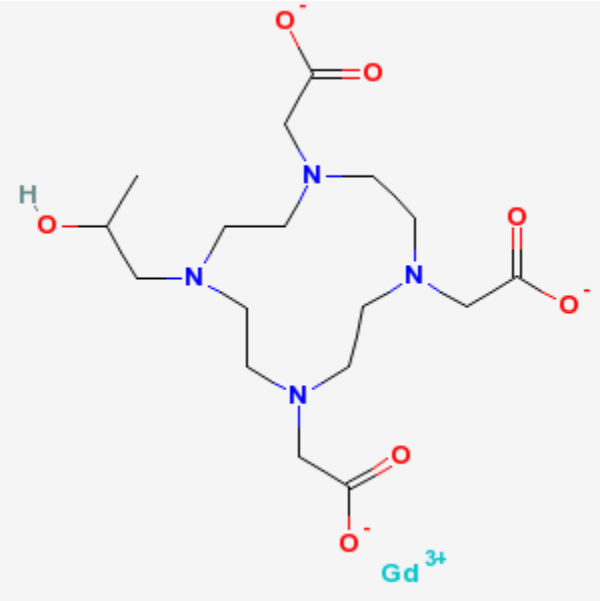
Gadoteridol
Gd-HP-DO3A

Created: October 07, 2005
Updated: November 18, 2005

Chemical name:	Gadoteridol
Abbreviated name:	Gd-HP-DO3A
Synonym:	ProHance®, SQ 32692, MOLI001032
Backbone:	Compound
Target:	Central nervous system, extracranial/extraspinal tissues
Mechanism:	Blood-brain barrier breakage, perfusion deficiency in extracranial/extraspinal tissues
Method of detection:	MRI
Source of signal:	Gadolinium
Activation:	No
***In vitro* studies:**	Yes
Rodent studies:	Yes
Other non-primate mammal studies:	Yes
Non-human primate studies:	Yes
Human studies:	Yes



Click on the above structure for additional information in PubChem [http://pubchem.ncbi.nlm.nih.gov/].

Background

[PubMed]

Gadoteridol (Gd-HP-DO3A) is a paramagnetic contrast agent of magnetic resonance imaging (MRI) developed for imaging the central nervous system (CNS) and extracranial/extraspinal tissues (1-4).

Paramagnetic contrast agents are generally metal chelates with unpaired electrons, and they work by shortening both T_1 and T_2 relaxation times of surrounding water protons to produce the signal-enhancing effect. At normal clinical doses of 0.1-0.2 mmol/kg, the T_1 effect tends to dominate (2, 3). Current agents are water-soluble compounds that do not cross the intact blood-brain barrier (BBB).They can be used to enhance signals of CNS tissues that lack a BBB (e.g., pituitary gland), extraaxial tumors (e.g., meningiomas), and areas of BBB breakdown (e.g., tumor margins) (5-8). In these cases, small or multiple CNS lesions are more clearly delineated with contrast enhancement. In addition, contrast enhancement can highlight vasculature, delineate the extent of disease, and

confirm the impression of normal or nonmalignant tissues. These contrast agents can also be used in a similar nonspecific manner to enhance contrast between perfused and nonperfused areas in other organs, such as the liver and myocardium (2, 3, 9).

Gadolinium (Gd), a lanthanide metal ion with seven unpaired electrons, has been shown to be very effective at enhancing proton relaxation because of its high magnetic moment and very labile water coordination (3, 4, 10-12). Gd-DTPA (gadopentetate dimeglumine) was the first intravenous MRI contrast agent used clinically, and a number of similar gadolinium chelates have been developed in an effort to further improve clinical efficacy, patient safety and patient tolerance. The major chemical differences among these Gd chelates are the presence or absence of overall charge, ionic or nonionic, and their ligand frameworks (linear or macrocyclic). Whereas Gd-DTPA is an ionic linear chelate, Gd-HP-DO3A has a macrocyclic tetraamine framework and is nonionic. Because of these differences, Gd-DTPA (0.5 M) possesses an osmolality of 1940 mOsmol/kg with a 1:3 ratio of Gd atoms to solute particles, but Gd-HP-DO3A in the same concentration has an osmolality of 630 mOsm/kg and a Gd:solute ratio of 1:1.

The commercial formulation of gadoteridol is available as a 0.5 M injection with a recommended dose of 0.1 mmol/kg(0.2 ml/kg) either as a rapid intravenous infusion or bolus injection for CNS or head/neck MRI imaging (1). A second dose of 0.2 mmol/kg (0.4 ml/kg) may be given up to 30 min after the first dose.

Synthesis

[PubMed]

The macrocyclic DO3A and R-DO3A ligands were synthesized by Dischino and colleagues (13) in 1991. There were several pathways for the synthesis of the DO3A core ligand. The most direct synthesis involved the alkylation of the commercially available unprotected cyclen, 1,4,7,10-tetraazacyclododecane, with chloroacetic acid to give a final yield of 26.2%. Several other multistep synthesis approaches were possible. The most productive approach (69% yield) appeared to be preparing the formyl cyclen, 10-formyl-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, tris-(1,1-dimethylethyl)ester, in which the protecting groups could be easily removed. In this approach, HP-DO3A was first prepared by reacting DO3A with *N*-(2-hydroxy-ethyl)-2-chloroacetamide in sodium hydroxide. HP-DO3A was then reacted with gadolinium oxide at pH 4.0 and 100^{o}C for 5 h. After preparative high performance liquid chromatography (HPLC) purification, the final yield of Gd-HP-DO3A was 43%.

The commercial preparation of Gd-HP-DO3A contains 279.3 mg of gadoteridol/ml with a pH of 6.5-8.0, viscosity of 1.3 cP at 37^{o}C, specific gravity of 1.140 at 25^{o}C, and an octanol:H_2O coefficient of −3.68 ± 0.02 (1).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The *in vitro* relaxivity value of Gd-HP-DO3A, $^{20}r_1$ (T_1 relaxivity at 20 MHz), was determined to be 3.7 ± 0.1 ($mM^{-1}s^{-1}$) with a Q (the number of simultaneously coordinated water molecules) = 1.3 ± 0.1 and a rotational correlation time(τ_r) of 57 ps (4). In comparison, the value of $^{20}r_1$ for Gd-DTPA was 3.8 ± 0.1 $mM^{-1}s^{-1}$.

An *in vitro* erythrocyte compatability test indicated that 0.5 M Gd-HP-DO3A did not appear to have any potential to hemolyze human erythrocytes (14). An acute cardiotoxicity study in the isolated rat heart model showed only small inotropic and electrophysiologic effects induced by Gd-HP-DO3A at 0.3-1.5 mmol/kg of body weight doses (15). The conditional stability constant (Log K' at pH 7.4) of Gd-HP-DO3A was 17.1 (4). In another qualitative comparison study of various Gd chelates, Gd-HP-DO3A was found to be kinetically very inert (transmetallation kinetics with Zn^{2+}) (16). Inhibition of the angiotensin-converting enzyme (ACE; a zinc- dependent metallopeptidase) by Gd-HP-DO3A was 7.7 ± 1.9 mM (LC_{50}) (17).

Animal Studies

Rodents

[PubMed]

The acute intravenous LD_{50}s (mmol/kg) for 0.5 M Gd-HP-DO3A were 11-14 in mice and >10 in rats (14). In a local tissue toxicity study using mice, Gd-HP-DO3A appeared to cause less tissue damage in response to extravascular extravasation than ionic contrast agents (18). Geschwind and colleagues (19) studied acute hemodynamic effects of contrast agents in rats and found that Gd-HP-DO3A at doses of 0.25-0.5 mmol/kg induced cardiovascular changes that were only slightly less profound than those produced by Gd-DTPA.

In rat biodistribution studies, Gd-153-labeled GD-HP-DO3A was largely distributed in extracellular space, renally excreted, and did not cross the BBB (20, 21). More than 90% of the dose appeared in the urine within 4 h of injection (22). Tissue concentrations indicated a linear function of injected doses in blood, skeletal muscle, and myocardium. MR signals (T_1-weighted, spin-echo pulse sequence) from imaging increased with increasing tissue concentrations up to 0.61 µmol/g in heart and 0.63 µmol/g in skeletal muscle. Above these concentrations, MR signals did not increase further. The residual whole-body Gd retention in mice and rats of Gd-HP-DO3A also appeared to be lower than that of Gd-DTPA (22, 23).

Using a rat brain gliosarcoma model, Runge and colleagues (24) demonstrated that Gd-HP-DO3A provided MRI enhancement in brain tissue with an altered BBB to allow identification of the implanted tumor lesion.

Other Non-Primate Mammals

[PubMed]

A 2-week intravenous study (0.5 M) in dogs indicated no treatment-related changes and no treatment-related lesions at dose levels of 0.25-1.5 mmol/kg (14). Only bleeding times and serum iron levels appeared to have slight transient changes after repeated doses. Gd-HP-DO3A at 1.0 M was maternotoxic in rabbits at doses of 6 mmol/kg. No neutrotoxicity was observed in rabbits with induced breakdown of the BBB for 6 weeks after receiving i.v. 0.3 mmol/kg of Gd-HP-DO3A (25).

Gd-HP-DO3A was rapidly cleared from the dog blood, and about 88% of the injected dose was excreted in the urine within 24-48 hours (22). With the use of MRI and direct brain ventricular injection in guinea pigs with induced hydrocephalus, Yamada and colleagues (26) found that Gd-HP-DO3A moved in the CSF in proportion to the CSF pressure. It was observed to clear from the lateral and third ventricles, but it was not observed to reach either over the convexity of the brain or adjacent to the superior sagittal sinus. The detectability of brain metastases with Gd-HP-DO3A was studied in a rabbit brain tumor model. The use of a higher dose (0.3 mmol/kg) appeared to improve metastatic lesion detectability from 30 ± 15% of 0.1 mmol/kg to 104 ± 10%. Other studies in rabbits and dogs showed that the use of this agent could also be valuable in other organ systems [PubMed].

Non-Human Primates

[PubMed]

The distribution of Gd-HP-DO3A in healthy rhesus monkeys was used in a number of studies as a control for comparison with newer MRI contrast agents [PubMed].

Human Studies

[PubMed]

In the United States, a Phase I clinical trial with 18 healthy male volunteers (18-40 years of age) showed that gadoteridol (0.05-0.3 mmol/kg) rapidly distributed from the vascular compartment to the extracellular fluid space, and it was excreted by glomerular filtration in the kidneys (27). About 94 ± 4.8% of the injected dose was excreted in the urine within 24 h. The elimination and distribution half-lives were independent of the doses used in the study. The mean distribution and elimination half-lives were 0.20 ± 0.04 and 1.57 ± 0.08 h, respectively. Adult patients (*n*=87) with intracranial tumors were studied in the phase II clinical trial to determine the safety of Gd-HP-DO3A at doses of 0.025, 0.05, 0.10, 0.15, 0.20 and 0.30 mmol/kg (10). Gadoteridol was well tolerated with no significant adverse reactions within the studied dose range.

The Phase III clinical trial of Gd-HP-DO3A, at a dose of 0.10 mmol/kg in the United States, was a multicenter (27 sites) study involving patients (*n*=411) suspected of having intracranial or spinal pathology (28). MRI imaging (1.5 Tesla MRI) was used to produce precontrast (both T_1- and T_2-weighted) scans and postcontrast (T_1-weighted) scans, and blinded evaluation was conducted by two readers. Improved contrast enhancements were observed in 62-83% of the cases, and in 43-76% of the cases, additional diagnostic information was provided. In comparison, the European Phase III multicenter trial with 151 patients using unblinded investigators showed improved contrast enhancement in 75% of cases with brain pathology and 64% of cases involving spine lesions (29). In a United States pediatric patient study, the agent was found to be equally safe and improved

contrast enhancement was present in 77% (*n*=22) of the cases (5). Comparison studies generally indicated that the clinical performance of Gd-HP-DO3A for CNS imaging was comparable with other commercially available agents (12, 30).

Runge and Parker (31) reported a worldwide clinical safety assessment of gadoteridol in 1997 that indicated a 6.6% incidence rate of total adverse events (nausea, taste perversion, headache, etc.) from 2656 administered injections in Europe and the United States. Gibby and colleagues (32) in 2004 found that Gd-HP-DO3A had a relatively low Gd retention in human bone tissue (0.466 ± 0.387 µg/g) after the administration of a clinical dose to eight patients.

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